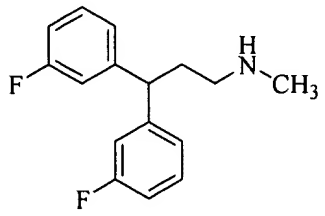
REMARKS/ARGUMENTS

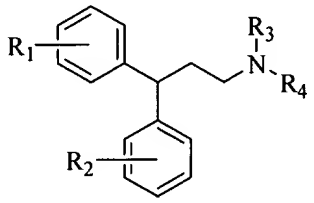
The Final office action mailed June 1, 2005, has been received and reviewed. Claims 5-6 and 21-27 are currently pending in the application. Claims 5-6 and 21-27 stand rejected. Claims 5 and 25-27 are amended herein. Claims 28 and 29 have been added. Applicant respectfully requests reconsideration of the application as amended herein and in light of the arguments presented below.

Background

In the present case, Applicant responded to a first office action with restriction requirement and provisionally elected compound 60 as an elected species. Compound 60 has the following structure and can be found in newly added claims 28 and 29.



Subsequently, claims 5-6 and 21-24 were rejected in an office action dated September 22, 2004, in view of Jones et al. (Journal of Medicinal Chemistry, 1971, Vol. 14, No. 2, pp. 161-4), on grounds that the reference teaches the use of 1,1-diphenyl-3-aminopropanes (more accurately called 3,3-diphenyl-1-aminopropanes) of the formula:



where "R1 is H, 3-F, 3-CF3, 2-Me, 2-MeO, 4-F, 4-Cl; R2 is H, 3-F, 3-CF3, 4-F, 4-Cl; R3 is CH3; R4 is H or CH3; or pharmaceutically acceptable salts (e.g. HCl, oxalate), as antidepressant agent that is useful for the treatment of depression (Table III; Experimental Section [at] pages 162-163)" (*see* page 3, second paragraph). The examiner also stated that "the teachings of Jones differs from the prior art by reciting a specific species, more particularly 3-F at X1 and X2 and

–CH3 or –H at R3" (*see* page 3, third paragraph (emphasis added)). The examiner then reasoned that

> "...it would have been obvious to a person skilled in the art at the time of the invention was made to arrive at the claimed invention since a person of ordinary skill in the art would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as the genus as a whole. One would have been motivated to combine the references and make the modification because they are drawn to the same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP § 2141.01(a)."

Id. (emphasis added). The examiner identified no other references in support of the rejection.

Applicant traversed the obviousness rejection and added dependent claims 25-27. In response to Applicant's new claims and arguments, the examiner issued an office action dated June 1, 2005, making the § 103 rejection final as to claims 5-6 and 21-27, but without addressing the limitations in claims 25-27.

Applicant respectfully traverses the rejection for the reasons set forth below.

35 U.S.C. § 103(a) Obviousness Rejection

Claims 5-6 and 21-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Jones et al. Applicant respectfully traverses the rejection on grounds that Jones et al. do not support a *prima facie* case of obviousness.

M.P.E.P. 706.02(j) sets forth the standard for a Section 103(a) rejection:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

An examiner bears the initial burden to factually support a *prima facie* case of obviousness. With no factual support, a *prima facie* case is absent and the applicant is under no obligation to submit evidence of nonobviousness (*see In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984); M.P.E.P.

§ 2142). A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention (*see W.L. Gore and Associates, Inc. v. Garlock, Inc.* 721 F.2d 1540 (Fed. Cir. 1983) *cert. denied*, 469 U.S. 851 (1984); M.P.E.P. § 2141.02).

The present obviousness rejection is improper for the following reasons. First, the rejection is ambiguous and unclear. Second, Jones et al. do not provide a *prima facie* case of obviousness. Third, the rejection does not specify the limitations found in the previously added dependent claims 25-27 and newly added claim 29. Each of the above grounds of traverse is discussed below.

A. The obviousness rejection is ambiguous and unclear.

The examiner has not satisfied the requirement to clearly explain the grounds of rejection. 37 C.F.R. § 1.104(b) and (c) require an examiner to clearly explain any grounds for claim rejection. M.P.E.P. §§ 706 and 707 specifically require that "'[w]henever, on examination, any claim for a patent is rejected, or any objection...made, notification of the reasons for rejection and/or objection together with such information and references as may be useful in judging the propriety of continuing the prosecution (35 U.S.C. 132) should be given."

The grounds of rejection are unclear first because the rejection is based on a comparison of the cited Jones et al. reference to "the prior art" (*see* page 3, fourth paragraph), without stating what "prior art" is being relied upon. This statement is indefinite and unclear because the law requires that the claimed invention be compared to the prior art. According to *Graham v. John Deere*, 383 US 1, 17 (1966), a proper inquiry of non-obviousness requires that, "[u]nder § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained" (emphasis added). In view of the fact that the Examiner incorrectly compares the prior art reference of Jones et al. to other prior art and fails to identify what prior art Jones et al. is being compared to, Applicant is unable to ascertain the substance of the rejection and respond in a meaningful way.

Second, the grounds of rejection are also unclear because the examiner appears to rely on a plurality of references (in addition to Jones et al.), but again fails to identify what other reference (other than Jones et al.) is being relied upon. Specifically, the office action states that "[o]ne would have been motivated to combine these references and make the modification

because they are drawn to [the] same technical fields . . ." (*see* page 3, fourth paragraph). However, no reference other than Jones et al. is cited, nor has the examiner explained what teachings of the prior art are being combined with Jones et al. in support of the rejection. Thus, Applicant submits that the obviousness rejection does not clearly explain the grounds for rejection.

In view of the fact that the office action does not identify or explain the relevance of the prior art being relied upon, Applicant respectfully submits that the examiner has not met the burden of establishing a prima facie case of obviousness. Applicant respectfully requests that the examiner clarify the grounds for the obviousness rejection and whether the examiner is relying solely on Jones et al., on a combination of references, or on other facts within the realm of the prior art not found in any published reference. Without the benefit of a clear statement of the grounds of rejection, the examiner has not met his burden of establishing a prima facie case of obviousness, and Applicant cannot properly respond. In the event that the examiner is relying on "facts within his or her knowledge" pursuant to 37 C.F.R. § 01.104(6)(3) and (d)(2), Applicant respectfully requests that the examiner provide an affidavit describing such facts and explaining the basis of the examiner's reliance on those facts. Applicant further requests that any future rejection be made non-final to permit a fair and proper opportunity to respond.

B. Jones et al. do not provide a *prima facie* case of obviousness.

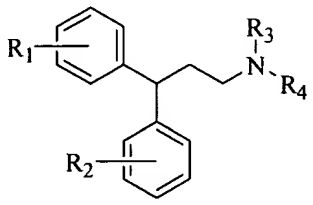
Notwithstanding the ambiguity and indefiniteness of the rejection, Applicant will attempt to address the issues raised by Jones et al. In addressing the issue of obviousness, the law is clear that a reference must suggest a modification to arrive at the claimed methods and give a reasonable expectation that the modification will be successful (*see* M.P.E.P. § 706.02(j), 2142; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention (*see W.L. Gore and Associates, Inc. v. Garlock, Inc.* 721 F.2d 1540 (Fed. Cir. 1983) *cert. denied*, 469 U.S. 851 (1984); M.P.E.P. § 2141.02).

Applicant respectfully submits that Jones et al. alone does not satisfy the above requirements for a *prima facie* showing of obviousness, because the examiner has not considered Jones et al. as a whole and has failed to consider the teachings in Jones et al. that lead away from the claimed invention. Specifically, as discussed in detail below, Jones et al. do not teach a genus

encompassing Applicant's elected species, subgenera, and genus claims. Jones et al. also do not teach structurally similar compounds with the limitations recited in the claimed invention or provide a motivation to obtain the claimed compounds with a reasonable expectation of successfully treating depression. Moreover, the office action does not address the limitations in claims 25-27 and newly added claim 29.

1. **Jones et al. do not teach a genus encompassing Applicant's claims.**

In the present case, the examiner has mischaracterized the scope of the genus taught by Jones et al., and has therefore improperly determined the "scope and content of the prior art" *Graham v. John Deere* (*see* 383 US 1,17 (1966)). Specifically, the examiner states that Jones et al. teach a genus of the formula:



where R1 is H, 3-F, 3-CF3, 2-Me, 2-MeO, 4-F, 4-Cl; R2 is H, 3-F, 3-CF3, 4-F, 4-Cl; R3 is CH3; R4 is H or CH3 (*see* page 3, second paragraph). The examiner argues that the Applicant's elected species and subgenera claims 22 and 24 are within the asserted genus and are obvious because a "species of the genus would have similar properties, and, thus, the same use as the genus as a whole" (*see* page 3, fourth paragraph). The examiner is silent with respect to the remaining pending claims.

A determination of patentability under 35 U.S.C. § 103 should be made upon the facts of the particular case in view of the totality of the circumstances (*see In re Dillon*, 919 F.2d 688, 692-93 (Fed. Cir. 1990) (en banc)). Use of *per se* rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 U.S.C. § 103 (*see* M.P.E.P. § 2144.08(II) *citing In re Brouwer*, 77 F.3d 422, 424 (Fed. Cir. 1996); *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995); *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994); *In re Devel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995)).

For the reasons set forth below, Applicant submits that Jones et al. does not teach a genus encompassing any of the instant claims including the elected species for the following reasons. Specifically, the examiner overstates the genus actually disclosed in Jones et al., which in effect misrepresents the actual teaching of Jones et al. In addition, contrary to the examiner's statement that Jones et al. provide motivation for the claimed compounds, Jones et al. actually teach away from the claimed invention.

a. <u>Jones et al. do not expressly teach the examiner's asserted genus.</u>

First, the examiner misstates the genus disclosed by Jones et al., which actually teaches a significantly narrower genus. This "genus" asserted by the examiner, however, does not accurately represent the actual teachings of Jones et al. Table III and the experimental section of Jones et al. disclose only 18 *alkane* compounds (shown below).

Compound Number	R1	R2	R3	R4
43	H	H	CH3	H
44	H	H	CH3	CH3
45	3-F	H	CH3	CH3
46	4-F	H	CH3	CH3
47	4-Cl	H	CH3	CH3
48	3-CF3	H	CH3	CH3
49	2-CH3	H	CH3	CH3
50	2-OCH3	H	CH3	CH3
51	3-F	3-F	CH3	CH3
52	4-F	4-F	CH3	CH3
53	3-CF3	3-CF3	CH3	CH3
54	4-Cl	4-Cl	CH3	CH3
55	4-F	4-Cl	CH3	CH3
56	4-F	4-F	CH3	H
57	4-Cl	4-Cl	CH3	H
58	H	H	cyclic	
59	H	H	cyclic	
60	H	H	cyclic	

The above table includes 18 specific 3,3-diphenyl-1-aminopropane compounds (as either their hydrochloride or oxalic acid salts), 15 of which are non-cyclic amine compounds and 3 of which are cyclic amine compounds (*see* Jones et al. pages 163-164). Excluding the cyclic amines

(which are not claimed in the present application), the remaining compounds include 7 different moieties for R1, 5 different moieties for R2, 1 moiety for R3, and 2 different moieties for R4. Each combination of the moieties for R1-R4 forms the basis for the examiner's genus based on the different possible moieties disclosed for each of the R1, R2, R3, and R4 groups. The examiner incorrectly assumes that any particular moiety of one position can be combined with any and all possible moieties at the other positions, and concludes that Jones et al. teach a genus of 70 compounds (7 x 5 x 1 x 2 = 70).

Jones et al., however, do not teach a genus of 70 compounds. Jones et al. disclose a total of only 18 compounds. Although the chemical formula V displayed above is shown in conjunction with Table III, Jones et al. proffer this structure solely for the purpose of figuratively illustrating the 18 compounds actually disclosed, and nothing more. In fact, Jones et al. expressly state that "[t]his paper is concerned with the synthesis of new compounds of the generic structures IV and V and their evaluation as potential antidepressants" (*see* page 161, first paragraph (emphasis added)). Also, the reference states that the researchers "*investigate[d]* the pharmacological properties *of compounds* of the general structures IV and V" (*Id.*). This statement clearly indicates that the "general structures IV and V" represent only those compounds actually investigated, *i.e.*, those compounds reported in Table III. The reference also uses a definite article ("the") when narratively referring to the reported compounds "the saturated compounds" and "the unsaturated series" (*see*, page 162, second paragraph (emphasis added)), further reinforcing that the general structures represent only those compounds actually synthesized and tested, and no others. Thus, the reference expressly states that the "generic structure" of formula V represents only those compounds appearing in Table III. The examiner cannot fabricate a genus of approximately 70 compounds from a list of 18 species.

The asserted genus is also improper because there is no teaching to support the examiner's position that formula V represents any compounds other than those specifically disclosed. Unlike a genus described in a patent or patent application, which often expressly teaches that the variables at each position may be combined with any possible variable at any other position, in all possible permutations, the Jones et al. reference is a technical document from a scientific journal that reports only specific compounds and contains no teaching or suggestion that the generic formula represents any compounds other than those specifically

disclosed. More particularly, Jones et al. provides no teaching of or support for combining particular moieties at one position with other moieties at another position, where such a combination is not found among the specific compounds disclosed. Thus, the examiner's inference that every moiety listed for each R group found in a species from Table III can be combined with any one of the moieties listed for a different R group is impermissible and results in a "genus" that is not supported by the teachings of Jones et al. Jones et al. do not provide any express teaching to support the examiner's genus.

The examiner's assertion that formula V represents compounds in addition to those found in Table III is therefore without merit and misstates the teaching of Jones et al.

b. Jones et al. teach away from the examiner's asserted genus.

Jones et al. not only fail to provide any express teaching to support the examiner's asserted genus, but also fail to provide any suggestion for doing so. In fact, Jones et al. actually teach away from the examiner's asserted genus.

The examiner has taken the position that since known antidepressants mentioned in Jones et al. (amitriptyline, imipramine, desipramine, and nortirptyline) reverse resperine-induced hypothermia (reserpine assay) at or below a value of 7, then a compound with a reserpine assay value of 7 or less would be expected to have potential antidepressant activity (*see* page 4, second paragraph). Specifically, the examiner points to Jones et al. compound 51 in Table III and compounds 28 and 29 in Table I which all have a reserpine assay value of 2 to support this position. The examiner concludes that "it is clear that compounds having halogen substituent(s), especially F or Cl, in the Ph rings and Me or two Me radicals substituent(s) at N demonstrate comparable or better antidepressant activity as the known antidepressants..." (*Id.*).

Jones et al. do not, however, support the examiner's conclusion, because the majority of compounds within the Table III genus lack antidepressant activity suggesting that compounds falling within that genus are more likely than not to lack antidepressant activity. In other words, the examiner failed to account for evidence that teach the opposite of the examiner's conclusion. For example, several compounds from Table III (reproduced below) that satisfy the examiner's definition (halogen substituted phenyl compounds with mono- or di-methyl substituted amine), but actually display reserpine assay values exceeding 7 which, according to the examiner's rationale do not teach antidepressant activity.

Compound Number	R1	R2	R3	R4	Reserpine Assay
55	4-F	4-Cl	CH3	CH3	100
47	4-Cl	H	CH3	CH3	50
54	4-Cl	4-Cl	CH3	CH3	50
52	4-F	4-F	CH3	CH3	10
56	4-F	4-F	CH3	H	10
57	4-Cl	4-Cl	CH3	H	Not reported
46	4-F	H	CH3	CH3	3
45	3-F	H	CH3	CH3	2
51	3-F	3-F	CH3	CH3	2

More specifically, compound 55 (where R1 and R2 are both 4-Cl and R3 and R4 are both CH3) has a reserpine assay value of 100. Compound 47 (where R1 is 4-Cl, R2 is H, and both R3 and R4 are CH3) has a reserpine assay value of 50. Likewise, compound 54 (where R1 and R2 are both 4-Cl and R3 and R4 are both CH3) has a reserpine assay value of 50. Compound 52 (where R1 and R2 are both 4-F and R3 and R4 are both CH3) and compound 56 (where R1 and R2 are both 4-F and R3 is CH3 and R4 is H) have a reserpine assay value of 10. Compound 57 (where R1 and R2 are both 4-Cl, R3 is CH3, and R4 is H) has an unreported reserpine assay value. Thus, of the 9 compounds meeting the examiner's structural definition, 6 have greater or unreported reserpine assay values than the reported known antidepressants and teach away from the examiner's conclusion. In view of this data, one skilled in the art would have no rationale basis to conclude that 3,3-bis(phenyl)-1-aminopropyl compounds having halogen substituent(s) in the phenyl rings and one or two N-methyl substituent(s) give comparable or better antidepressant activity than known antidepressants. The weight of these examples suggests that the compounds in Table III (and the examiner's asserted genus) are generally less active or inactive for treating depression.

In view of the fact that Jones et al. disclose only 15 non-cyclic species in Table III, and more examples fail to satisfy the reserpine assay test on which the examiner relies, Applicant respectfully submits that the reference does not teach a genus encompassing the Applicant's claims. In the absence of a genus encompassing the Applicant's claims, the examiner has not met the burden of establishing a *prima facie* case of obviousness and the rejection should be withdrawn.

2. Jones et al. do not suggest structurally similar compounds having the same properties.

The above argument establishes that the genus asserted by the examiner is narrower than the examiner asserts, and does not encompass Applicant's claims. Assuming that the actual genus of Jones et al. excludes Applicant's claimed compounds, Applicant submits that Jones et al. do not suggest structurally similar compounds would be expected to have the same properties. Thus, Jones et al. do not support a *prima facie* case of obviousness because it does not teach or suggest structurally similar compounds that have the same property of treating depression and, therefore, does not provide a reasonable expectation that Applicant's claimed compounds will treat depression.

Obviousness can only be established by modifying the teachings of a reference where there is some teaching, suggestion or motivation to do so found explicitly or completely in that or another reference (*see* M.P.E.P. § 2143.01). While structural similarity may serve as the basis for an obviousness rejection, there must nevertheless be a suggestion to modify the reference with a reasonable expectation of success (*see* M.P.E.P. § 2144.09). In addition, a prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention (*see W.L. Gore and Associates, Inc. v. Garlock, Inc.* 721 F.2d 1540 (Fed. Cir. 1983) *cert. denied*, 469 U.S. 851 (1984); M.P.E.P. §§ 2141.02 and 2132.02(VI)).

a. Jones et al. fail to provide motivation to arrive at the Applicant's claimed methods to treat depression.

The examiner has argued that the claimed compounds are obvious because "compounds having halogen substituent(s), especially F or Cl, in the Ph rings and Me or two Me radicals substituent(s) at N demonstrate comparable or better antidepressant activity as the known antidepressants..." (*see* page 4, second paragraph). In support of this conclusion, the examiner argues that Applicant's elected species (having H at R4) would have been obvious in view of Jones et al. compound 51 (which differs structurally from the elected species by having CH3 at R4), on grounds that one skilled in the art would expect the substitution of CH3 with H at R4 to result in a compound having anti-depressant activity. In support of this proposition, the examiner argues that Jones et al. teach an analogous substitution of CH3 with H in two *alkene* compounds, compounds 28 (having H at R4) and 29 (having CH3 at R4), both of which have reserpine assay

values of 2, indicative of antidepressant activity. Compounds 28, 29, and 51 are summarized below.

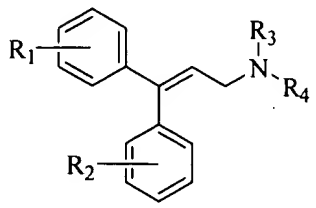
Compound Number	R1	R2	R3	R4	Reserpine Assay
alkene 28	3-F	3-F	CH3	H	2
alkene 29	3-F	3-F	CH3	CH3	2
alkane 51	3-F	3-F	CH3	CH3	2

The examiner reasons that because the two *alkene* compounds 28 and 29 (which differ only by a substitution of H or CH3 at R4) both have antidepressant activity, then the *alkane* compound 51 (having CH3 at R4 and anti-depressant activity) must therefore suggest that the alkane compound of the elected species (having H at R4) also possesses anti-depressant activity. Specifically, the examiner argues that "one having ordinary skill in the art would have expected as taught by the Compounds 28 and 29 that substitution of H at R4 for CH3 would not alter the analogous properties of the Compounds 51 of the Jones [reference] due to close structural similarity of the compounds" (*see* page 5, first paragraph).

Applicant submits, however, that the examiner's argument is not supported by the experimental data set forth in Jones et al. As noted above, the examiner's conclusion ultimately rests on the assumption that there is a correlation of anti-depressant activity between the *alkene* compounds 28 and 29, which differ only by H and CH3, respectively, at R4. The examiner's conclusion further rests on the assumption that there must also be a correlation of anti-depressant activity between the *alkane* compounds 51 and the elected species, which also differ only by CH3 and H, respectively, at R4. While the above assumptions may appear facially reasonable and valid, the teachings of Jones et al. contradict the assumptions. As demonstrated below, anti-depressant activity of *alkene* compounds is not necessarily predictive of anti-depressant activity of corresponding *alkane* compounds.

Jones et al. provide a large body of data that contradict the examiner's assumptions that anti-depressant activity of the alkane compound 51 having CH3 at R4 is predictive of anti-depressant activity of the alkane compound of the elected species having H at R4. The data of Jones et al. in fact teach that the *alkane* compounds have disparate and unpredictable reserpine assay values compared to their *alkene* counterparts, and also teach that substituting CH3 for H in an alkane compound does not result in a substantially similar reserpine assay value.

Applicant first submits that the examiner has not considered the reference as a whole and failed to consider evidence teaching that the *alkene* compounds of Table I having the formula:



teach away from corresponding *alkane* compounds having antidepressant activity. And, in an effort to illustrate the fallacy of the examiner's logic, Applicant will cite several examples involving *alkene* compounds that demonstrate the error of the examiner's logic.

First, the data of Jones et al. demonstrate that N-mono- or di-methyl compounds do not necessarily have antidepressant activity. Specifically, as shown in the table below, Jones et al. teach that a*lkene* compounds 31 (having 4-Cl at R1 and R2, CH3 at R3, and H at R4) and 32 (having 4-Cl at R1 and R2, and CH3 at both R3 and R4) have reserpine assay activity of 2 and 3, respectively, indicative of anti-depressant activity. In contrast, *alkane* compound 54 (which has 4-Cl at R1 and R2, CH3 at R3, and CH3 at R4) does not have reserpine activity. Compound 57 (which differs from compound 54 only by H at R4) does not report reserpine assay results.

Compound Number	From Table	R1	R2	R3	R4	Reserpine Assay
alkene 31	I	4-Cl	4-Cl	CH3	H	2
alkene 32	I	4-Cl	4-Cl	CH3	CH3	3
alkane 57	III	4-Cl	4-Cl	CH3	H	Not reported
alkane 54	III	4-Cl	4-Cl	CH3	CH3	50

Thus, even though the alkene compounds have anti-depressant activity, the alkane compounds do not. In fact, compound 54 has nearly a 17-fold increase in reserpine assay value compared to compound 32! The reported reserpine assay value of 50 is more than 7-fold greater than the reserpine assay value for the least active antidepressant (imipramine). This example illustrates that anti-depressant activity of *alkene* compounds does not reasonably predict anti-depressant activity of corresponding *alkane* compounds. In view of this example, one skilled in the art could not have been able to reasonably expect that the alkane compounds of Table III (having halogen

substituents in the phenyl rings and one or two methyl substituents) would be useful in treating depression.

Second, the data in Jones et al. also demonstrate that N-mono- or di-methyl compounds do not necessarily have antidepressant activity. Specifically, as shown in the table below, Jones et al. teach that *alkene* compounds 18 (having 4-Cl at R1, H at R2, CH3 at R3, and H at R4) and 19 (having the same groups at R1, R2, and R3, but having CH3 at R4) both have reserpine assay results indicative of anti-depressant activity. In contrast, *alkane* compound 47 (also having the same groups at R1, R2 and R3, but having CH3 at R4) does not have anti-depressant activity.

Compound Number	From Table	R1	R2	R3	R4	Reserpine Assay
alkene 18	I	4-Cl	H	CH3	H	0.7
alkene 19	I	4-Cl	H	CH3	CH3	3
alkane 47	III	4-Cl	H	CH3	CH3	50

Thus, the *alkane* compound 47 does not have substantially similar reserpine assay activity compared to its *alkene* counterpart. In fact, compound 47 has nearly a 17-fold increase in reserpine assay value compared to compound 19. The reported reserpine assay value of 50 is more than a 7-fold greater than the reserpine assay value for the least active antidepressant (imipramine). Thus, this example further supports Applicant's contention that anti-depressant activity of *alkene* compounds is not predictive of anti-depressant activity of corresponding *alkane* compounds, and that one cannot reasonably expect that compounds structurally similar to those found in Table III (having halogen substituents in the phenyl rings and one or two methyl substituents) can be used to treat depression.

Third, the data in Jones et al. further demonstrate that one would not expect that compounds having CH3 at either R3 or R4 to have antidepressant activity. As shown in the table below, Jones et al. teach that *alkene* compounds 25 (having 4-F at R1 and R2, and CH3 at R3, and H at R4) and 26 (having the same moieties at R1, R2, and R3, but having CH3 at R4) both have reserpine assay results indicative of anti-depressant activity. In contrast, *alkane* compounds 56 and 52 (which have the same moieties at R1, R2, but differ by having H and CH3 at R4, respectively) do not have anti-depressant activity.

Compound Number	From Table	R1	R2	R3	R4	Reserpine Assay
alkene 25	I	4-F	4-F	CH3	H	3
alkene 26	I	4-F	4-F	CH3	CH3	3
alkane 56	III	4-F	4-F	CH3	H	10
alkane 52	III	4-F	4-F	CH3	CH3	10

The *alkane* compound 52 does not have identical or substantially similar reserpine activity compared to its *alkene* counterpart 26. In fact, compound 52 has a greater than 3-fold increase in reserpine assay value compared to compound 26. Furthermore, compound 56 has a greater than 3-fold increase in reserpine assay value compared to compound 25. And both *alkane* compound's reserpine assay values exceed the reserpine assay value for the least active antidepressant (imipramine). Again, the above data demonstrate that the *alkane* compounds do not have anti-depressant activity, even though the "analogous" *alkene* compounds do. Therefore, this example shows that one cannot reasonably expect that compounds structurally similar to those found in Table III (having halogen substituents in the phenyl rings and one or two methyl substituents) can be used to treat depression.

Fourth, Jones et al. also disclose data that demonstrate that compounds having CH3 at R3 or R4 do not have antidepressant activity. Significantly, as shown in the following table, *alkene* compound 34 (having 4-Cl at R1, 4-F at R2, and CH3 at both R3 and R4) and *alkane* compound 55 (having 4-F at R1, 4-CL at R2, and CH3 at both R3 and R4) *both* do <u>not</u> have anti-depressant activity.

Compound Number	From Table	R1	R2	R3	R4	Reserpine Assay
alkene 34	I	4-Cl	4-F	CH3	CH3	100
alkane 55	III	4-F	4-Cl	CH3	CH3	100

While the *alkane* compound 55 has identical reserpine activity compared to its *alkene* counterpart, both compounds have reserpine assay values that represent a 14-fold increase in reserpine assay value above the least active antidepressant (imipramine). Thus, this example shows that one cannot reasonably expect that compounds structurally similar to those found in Table III (having halogen substituents in the phenyl rings and one or two CH3 substituents) can be used to treat depression.

Finally, as previously argued in the Applicant's response to the September 22, 2004 office action, the Applicant asserts that Jones et al. expressly teach *against* the *alkane* compounds of Table III having anti-depressant activity. The reference states "the saturated compounds are in general marginally less active..." (*see* Jones et al. page 162, first full paragraph (emphasis added)). Thus, the reference itself teaches away from modifying the alkane compounds in Table III.

Taken together, the weight of the comparative examples 1-4 explained above, in contrast to the sole example (compounds 28, 29, and 51) relied on by the examiner, teach that one skilled in the art cannot reasonably expect that compounds structurally similar to those found Table III can be used to treat depression. And it is not clear that alkane compounds having halogen substituents, especially F or Cl, in the phenyl rings and one or two methyl substituents at N treat depression. Thus, the obviousness rejection should be withdrawn.

b. The compounds disclosed in Jones et al. do not predict that the compounds of the claimed invention have utility in treating depression.

The comparative examples discussed above also show that the alkane compounds in Table III have unpredictable properties, and as such, do not provide a reasonable expectation that the compounds of the claimed invention would be successful in treating depression.

A reference must provide a reasonable expectation that a change to arrive at Applicant's claims will nevertheless result in a similar property (*see* M.P.E.P. § 2143.02). If the technology is unpredictable, it is less likely that structurally similar compounds will render claimed compounds (and their methods of use) obvious (*see* M.P.E.P § 2144.08(II)(A)(4)(e)).

The examiner states that while compounds disclosed in Table III show "some variations in their potential antidepressant activity...there is no doubt that substitution in the phenyl rings with halogen, especially F or Cl, and substitution in N with CH3 and/or H preserves the antidepressant activity of the compounds"(*see* page 5, second full paragraph, (emphasis added)).

The examiner's conclusion is not supported because the compounds disclosed by Jones et al. do not suggest that those compounds and structurally similar compounds predictably treat depression. In fact, more examples from Table III exceed the reserpine assay threshold of 7 (indicative of lack of activity in treating depression) than satisfy it. Of the 9 compounds from

Table III that satisfy the examiner's structural definition (listed below), only 3 demonstrate anti-depressant activity.

Compound Number	R1	R2	R3	R4	Reserpine Assay
57	4-Cl	4-Cl	CH3	H	Not reported
47	4-Cl	H	CH3	CH3	50
54	4-Cl	4-Cl	CH3	CH3	50
55	4-F	4-Cl	CH3	CH3	100
52	4-F	4-F	CH3	CH3	10
56	4-F	4-F	CH3	H	10
45	3-F	H	CH3	CH3	2
46	4-F	H	CH3	CH3	3
51	3-F	3-F	CH3	CH3	2

Compound 57 does not have a reported reserpine assay value, and thus there is no suggestion it possesses anti-depressant activity. Compounds 47, 54, and 55 have reserpine assay values of 50 or greater, far outside the range required to demonstrate antidepressant activity, and at least a 7-fold level greater than that of imipramine. Compounds 52 and 56 both have a reserpine assay value of 10 which also exceeds the imipramine level and threshold the examiner relies upon for suggesting antidepressant activity. Although the remaining 3 compounds (45, 46, and 51), have a reserpine assay value of 3 or less, compounds 45 and 46 each have one unsubstituted phenyl ring, unlike the compounds in the instant claims. Only compound, 51, upon which the examiner's relies in support of the rejection, shows anti-depressant activity. Thus, six of the nine compounds having halogen substituted phenyl and one or two methyls at N do not meet the examiner's test for exhibiting potential antidepressant activity. Using classic "hindsight" reconstruction, the examiner has selected and focused solely on the single example supporting the rejection, while ignoring the other examples that teach away from the claimed invention. Accordingly, there is no predictability observed from the compounds of Table III to determine when structurally similar compounds will treat depression.

None of the other alkene compounds in Table I provide predictability when assessing structurally similar compounds might treat depression. The compounds in Table I are all alkenes and, as a separate class of compounds, cannot provide a reasonable expectation of success. Jones acknowledges this distinction when it identifies Table I compounds as 1,1-diphenyl-3-

aminoprop-1-enes (although they are more accurately named 3,3-diphenyl-1-aminoprop-2-enes). This distinction is made by the reference because the alkenes are more active than the alkanes (*see* page 162, second paragraph). On the other hand, the compounds from Table III are 3,3-diphenyl-1-aminopropanes. Therefore, the examiner's reliance on the data in Table I, particularly compounds 28 and 29, in support of the obviousness rejection is inappropriate as that data comes from a different class of compounds.

Even if the *alkane* compounds from Table I were relevant (again, Applicant insists they are not), they too give unpredictable assay results and do not provide the required motivation or expectation of success. The *alkene* compounds in Table I display a wide range of activity. Fourteen compounds are reported to have a reserpine assay value of 50 or greater (*e.g.*, compounds 1-4, 8-14, 30, 33, and 34), in excess of the reserpine assay threshold of 7. Even though some compounds display a reserpine assay value of 1 or less (*e.g.*, compounds 15-18, desimipramine, and nortriptyline), collectively, the assay data for all of the *alkene* compounds demonstrate the compounds' unpredictable property for treating depression. Thus, the alkene compounds reported in Table I are unpredictive to determine when *alkane* compounds might treat depression.

To summarize, both the alkane and alkene compounds disclosed in Jones et al. give inconsistent reserpine assay values and, therefore, are unpredictable to assess potential antidepressant activity of non-disclosed compounds. The examiner's obviousness rejection is improper because the implicit teaching of Jones et al. do not create a reasonable expectation that the compounds in the instant claims will treat depression and the rejection should be withdrawn.

C. Jones et al. do not teach the limitations of claims 25-27 and newly added claim 29.

A *prima facie* obviousness rejection must teach or suggest all of the claim limitations (*see* M.P.E.P. § 2142). The M.P.E.P. § 707.07(i) states that "[i]n every office action, each pending claim should be mentioned by number, and its treatment or status given." Further, "every limitation of a claim must be considered" (*see* M.P.E.P. § 2144.08; *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995)).

Because the examiner failed to provide any explanation for the rejection of dependent claims 25-27, the rejection should be withdrawn particularly with respect to these claims and newly added claim 29.

Applicant added dependent claims 25-27 in response to the September 22, 2005 non-final office action. The claims commonly recite that the recited compounds display activity at both the serotonin reuptake and NMDA receptor sites. The present office action failed to articulate any position with respect to the limitations present in claims 25-27 and newly added claim 29. Accordingly, there is no teaching or suggestion that the claimed compounds display activity at both receptor sites and result in the uses as claimed.

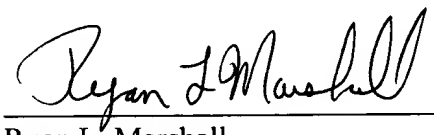
The examiner has failed to state a *prima facie* obviousness case as to claims 25-27 and newly added claim 29 and the rejection as to these claims should be withdrawn.

CONCLUSION

Applicant traverses the obviousness rejection because the rejection is unclear, Jones et al. do not suggest a genus encompassing Applicant's claims, Jones et al. do not suggest modifying its compounds with a reasonable expectation for successfully treating depression, and, the rejection does not specify the limitations found in claims 25-27 and 29.

Claims 5-6 and 21-29 are believed to be in condition for allowance, and an early notice thereof is respectfully solicited. Should the examiner determine that additional issues remain which might be resolved by a telephone conference, please contact the Applicant's undersigned attorney.

Respectfully submitted,



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